IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: VAN GELDER=1A

In re Application of:	)	Conf. No.: **8291**
Joel M. VAN GELDER et al	)	Art Unit: 4173
I.A. Filing Date: 02/06/2005 371(c) Date: August 7, 2006	)	Examiner: M.L. Sznaidman
U.S. Appln. No.: 10/588,554	)	Washington, D.C.
For: HEPARANASE INHIBITORS AND USES THEREOF	)	May 2, 2008

REPLY: REQUEST FOR RECONSIDERATION

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, **Mail Stop: Amendment**
401 Dulany Street
Alexandria, VA 22314

Sir:

The Official Action of December 4. 2007, has been carefully studied. Filed herewith is a petition for two months' extension of time and the petition fee. No amendments being presented, the previously pending claims are still pending, both examined and withdrawn.

The present invention defines not only novel and non-obvious subject matter, i.e. no prior art has been applied against applicants' claims, but also applicants' claims meet all the requirements of Section 112, and therefore should be allowed. Favorable reconsideration and allowance are respectfully urged.

As briefly noted above, no rejections have been imposed on the basis of any prior art. Applicants accordingly understand that applicants' claims are deemed to define novel and unobvious subject matter under Sections 102 and 103, and applicants are proceeding in reliance thereof.

As regards the presently non-elected and withdrawn claims, the Office Action indicates that there is presently "no **allowable** generic or linking claim" [emphasis added]. Applicants on the other hand maintain that the generic or linking claims are patentable, and therefore allowable, and should be allowed for the reasons pointed out below. Applicants respectfully maintain the qualifications set forth in the reply of November 1, 2007.

All the examined claims, namely claims 1, 16-18, 55, 57, 58, 138 and 139 have been rejected under the first paragraph of Section 112 "as failing to comply with the enablement requirement." This rejection is respectfully traversed.

Based on previous decisions, eight factors are raised as "factors that may be considered in determining whether a disclosure would require undo experimentation" and thus fail to meet the enablement requirement. Applicants address and traverse below the main arguments set forth in the Office Action in view of the stated eight relevant factors:

1. The nature of the invention, state and predictability of the art and relative skill of those in the art

Referring to the nature of the present invention, the examiner stated: "The invention relates to a method for treatment of a disease or disorder (melanoma is the species elected) caused by or associated with heparanase catalytic activity, said method comprising administering to a patient in need an effective amount of heparanase inhibitor of the general formula Id". Thus, according to the examiner, the relevant skilled person with whom the invention is most nearly connected would generally be a physician with an M.D. and several years of experience.

The examiner alleges that the above two factors (nature of the invention and the skilled person) are outweighed by the unpredictable nature of the art. Backing such arguments with several court cases, the examiner states that the invention relates to physiological activity, "and physiological activity is considered to be an unpredictable factor...[and] one skilled in the chemical and biological art cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances". Also, according to the examiner, "because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable". The

examiner is thus of the opinion that in view of the high unpredictability of the factors involved, the disclosure of the present application is not sufficiently enabling for the skilled person (a physician) to be able to carry out the invention.

The examiner further cites several publications, as illustrative of the state of the art for treating cancer in general, to show that the prior art does not disclose the use of small molecules as heparanase inhibitors, that no small molecule inhibitors have reached clinical trials and, therefore, the art is highly un-predictive with respect to small molecule heparanase inhibitors for the treatment of cancer.

At the end of section 1 of the Office Action, the rejection concludes: "These articles plainly demonstrate that the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers or different types of diseases. There are also no examples of small molecule heparanase inhibitors in the prior art for any of the following cases: 1- correlation of the in vitro inhibition and efficacy in humans, 2- there are very few examples correlating in vivo inhibition and efficacy in animals, and 3- there are

no examples of correlation between efficacy in animal models and efficacy in humans."

Applicants believe and respectfully submit that the position expressed in the rejection is unacceptable and not logical. If the idea is that experiments in humans have to be presented or at least be shown to exist in the art for related compounds, this is a requirement beyond what the law requires and beyond the authority of the PTO. The examiner is not authorized to act on behalf of the FDA, and has no authority to require that clinical trials must be conducted and used as evidence to provide enablement for method of treatment claims. Any further testing required would be routine, and this is perfectly acceptable under Section 112, noting MPEP 2164.06. As pointed out below, the PTO has not met the burden imposed by MPEP 2164.04.

Experiments established in recognized animal models have routinely served as the starting point for clinical trials later on and have led to the development of successful drugs that received FDA approval. Moreover, as applicants show herein below, for the purpose of evaluating new drug candidates, even *in vitro* test results, obtained from established *in vitro* model systems, suffice. There should be no doubt whatsoever of countless examples of US patents granted for drugs now marketed that are supported in the

description by results obtained from *in vitro* and/or in animal models such as those described in the present application.

The purpose of using the compounds of the invention is inhibition of the catalytic activity of heparanase, noting that such activity plays a major role in normal and diseased processes such as angiogenesis, inflammation, wound healing and tumor cell invasion, principally through action on the extracellular matrix (ECM). Heparanase activity is not specific to tumor cells. The compounds of the invention are not expected to directly destroy the cancerous cells. Rather, tumor growth inhibition will result from arresting the formation of new blood vessels in the tumor's vicinity. Metastasis is therefore expected to be inhibited by the small molecule inhibitors as a result of inhibiting cell invasion.

The heparanase inhibitors do not have to be cytotoxic to the tumor cells. Thus, the relevant *in vitro* assay for testing their functionality should comprise an enzymatic inhibition assay and an invasion inhibition assay. Because the drug candidates affect the tumor-associated vasculature rather than the tumor cells, the chances for a drug resistance during therapy are very small.

The inventors/applicants have provided evidence that should be considered sufficiently supportive of the present claims, as is shown below.

The heparanase inhibition activity of the compounds of the invention was performed by the *in vitro* dimethylmethylene blue (DMB) assay as described in item (a) on pages 65-66 and Example 23, page 70 of the description, and results (IC_{50} values) are depicted in the table in Appendix A. The ability of the compounds of the present invention to inhibit cell invasion was determined quantitatively by the *in vitro* Endothelial Cell Migration assay using an angiogenesis system kit, as described in item (c), page 67 and Example 23. The assay kit consists of a membrane uniformly coated with matrigel, which serves as a reconstituted authentic basement membrane *in vitro*. The results are depicted in Appendix A

In order to illustrate the state of the art for treating cancer in general, the examiner cited the documents of Gura and Johnson et al (Johnson):

Gura (Science, 1997, 278:1041-1042). According to the rejection, Gura teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile, and further teach that since formal screening began in 1955, many thousand of drugs have shown activity in either cell or animal models, but only 39 have actually been shown useful for chemotherapy.

Gura reviews model systems used up to 1997 for identifying new drugs, discusses their drawbacks, and outlines

the desired properties which will be required from future systems. According to Gura, "The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." The models referred by Gura are xenograft models, i.e., human tumors transplanted in animals, that were employed at the time for testing candidate cytotoxic drugs, mainly tumor-specific compounds aimed at destroying the cells of the specific cancer modeled. Lack of predictability stemmed, according to Gura, from, e.g., the fact that animals do not handle the drugs exactly the way the human body does, and/or the tumors "behave" differently in humans and some testing animals. The *in vitro* (cell cultures) models were problematic "partly because cell cultures provide no information about whether a drug will make it to the tumor cells".

The unpredictability associated with the *in vitro* and *in vivo* models used at the time to test cytotoxicity of tumor-specific candidate drugs is ascribed to the absence of faithful representations of carcinogenesis. Gura holds the general idea that a tumor's drug sensitivity may be linked to the genetic mutations the tumor carries, and therefore attempts should be made to use cells with comparable mutations to identify better chemotherapeutic agents. The required solution is therefore to address "the subtle genetic and cellular changes that lead a cell toward cancer, to create

cultured cells or animal models that accurately reproduce these changes".

Gura concludes, optimistically: "The future of cancer drug screening is turning almost exclusively toward defining molecular targets. If the approach works, drug developers would finally have an easy way to identify promising cancer drugs, and cancer patients might have an array of new treatments".

Gura then describes the improved screening approach adopted by the National Institute of Cancer (NCI) in testing drug candidates on a panel of 60 human cancerous cell lines, by reclassifying this panel to subsets based on tumor cell type and the type of genetic defects the cells carry.

It is to be noted that tumor-specific models finely tuned to display specific molecular defects associated with a particular type of cancer are not relevant to the compounds of the present invention. Again, the present compounds are not used for killing specific cell types, they are not intended to be tumor-type specific and therefore are not aimed against defined molecular targets involved in carcinogenesis.

The approach used by the present inventors/applicants does not relate to the genetic and cellular causes that lead to carcinogenesis and development of particular types of cancers, but rather addresses the inhibition of heparanase activity, such activity being the

basis of the mechanisms leading to metastasis and angiogenesis involved with most types of cancer. Therefore, the models discussed by Gura and the problems associated with them, and even the improved tumor-specific xenografts models and cell lines screening method mentioned, are not relevant to the present case, and the document by Gura is not a relevant illustrative of the state of the art as related to the present invention.

Johnson et al. (British Journal of Cancer, 2001, 84:1424-1431). According to the rejection, this document teaches that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer.

Johnson discusses the relationships between drug activity in NCI preclinical *in vitro* and *in vivo* models and early clinical trials. The candidate compounds disclosed in this article are all cytotoxic to tumor cells *in vitro* and aimed at directly destroying cancerous cells, therefore rendering the models discussed therein and the types of existing and future tests not relevant to the present invention. Thus, contrary to the examiner's opinion, and as explained above regarding the Gura disclosure, Johnson is not relevant for illustrating the state and predictability of the art as regards the present invention.

Regardless of its irrelevancy as noted above, applicants would nevertheless like to comment on the Johnson disclosure as follows: Johnson reports on an assay in which the *in vivo* activity of 39 known (standard) anti-cancer agents in a particular histology did not closely correlate with activity in the same human cancer histology, casting doubt on the correspondence of the pre-clinical models to clinical results. However, Johnson reports that for some of the 39 standard compounds that presented *in vivo* activity in at least one-third of the tested xenograft models, there was correlation with ultimate activity in at least some Phase II trails.

Also reported in this document are improved xenograft tumors developed by Fiebig, which retain characteristics similar to the clinical specimens and when treated with the same standard 39 agents, the response of these xenografts in comparison to patient tumors was 90% for sensitive and 97% for non-responding tumors, respectively.

Johnson therefore concluded that activity in multiple xenograft models is a useful predictor of clinical activity (page 1430, first column, first paragraph in the Discussion), and "an efficient means of predicting activity in in vivo models remains desirable for compounds with anti-proliferative activity in vitro". Furthermore, "The 'performance features' of compounds that have been evaluated

in the 'empirical' scheme may be of value in serving as a baseline against which newer compounds and models may be computed" (page 1425, end of first paragraph on the left column). Considering Johnson "as a whole" does not support the conclusion of the rejection.

In the Discussion section, Johnson et al state as follows:

> "The results... may be taken to argue against the use of activity in an empirically selected xenograft model to predict activity in the same histologic type of cancer in the clinic, and indeed that result has influenced the current philosophy underlying NCI's drug discovery and development program...Nonetheless, definition of an active agent in xenografts would allow optimization of schedule, assessment of molecular target endpoints, and increase the probability of clinical activity. It is therefore beneficial to have the ability to select agents with a likelihood of xenograft activity using a rapid and inexpensive test... consideration of the 'baseline' experience of an empirically oriented drug discovery program might usefully benchmark the type of compounds suitable for advancement to such models."

The conclusion drawn from the disclosures of Johnson and Gura is that problematic predictability of clinical activity is not due to an inherent unsuitability of *in vitro* and *in vivo* models for screening potential candidates for clinical use. The lack of sufficient correlation between *in vitro* and *in vivo* models versus clinical results is related to the models existing then (up to 1997) and their failure to display specific molecular targets involved in carcinogenesis, and to the testing strategy applied. Improvements in model

design and testing methodology would, according to the art, and in fact did, improve to a large extent the predictability potential of the models and the correlation between the models and the clinic. The preclinical use of *in vivo* models as well as *in vitro* models is irreplaceable and provides valuable information.

Regarding more specifically the treatment of different types of cancer with inhibitors of heparanase, the examiner cited 3 more documents:

Ishida et al. (The Journal of Antibiotics, 2004, 57:136-142), was cited as allegedly teaching that "most heparanase inhibitors reported by now (February 2004) are derivatives of sulfonated oligosaccharides similar to the substrate Heparan Sulfate, and not low molecular weight compounds (see page 136, column 2, second paragraph)".

Courtney et al. (Bioorganic and Medicinal Letters, 2004, 14:3269-3273), was cited as allegedly teaching that "even though Heparanase offers an attractive drug target, progress in this area has been limited by the current available repertoire of inhibitors. The most advanced inhibitor is PI-88 (a highly sulfonated mannan oligosaccharide), which is currently in Phase II clinical trials (and so far the only known heparanase inhibitor in clinical trials, see page 3269 first paragraph). So there are

still no small molecule inhibitors of heparanase in human trials for the treatment of any type of cancer".

McKenzie (British Journal of Pharmacology, 2007, 151:1-14) is cited as allegedly showing that there are very few small molecules available as heparanase inhibitors, and in only one case they show animal data in a B16-BL6 melanoma tail vein model. According to the examiner, McKenzie also mentions, regarding another group of small molecule heparanase inhibitors, that unfortunately there is no published data on the efficacy of any of the small molecule inhibitors in animal studies, hence it remains to be seen whether these compounds will actually have efficacy *in vivo*.

Contrary to the examiner's assertion, small molecule heparanase inhibitors had been proposed for treatment of human metastasis more than 10 year before the present application was filed. Prior art disclosing the synthesis and use of small molecule inhibitors of heparanase activity is listed in the Background section of the present application, on pages 3 and 4. Thus, for example, derivatives of siastatin B were synthesized by Nishimura et al (Nishimura et al., 1994, J. Antibiot. 47:101-107).

Nishimura et al synthesized a trifluoroacetamide analogue of siastatin B, (3S,4S,5R,6R)-6-(trifluoroacetamido)-4,5-dihydroxy-3-piperidine carboxylic acid. This compound, as well as its diastereomer (3R,4R,5R,6R)-6-(trifluoroacetamido)-

3,4,5-trihydroxy-3-piperid inecarboxylic acid, showed marked inhibitory activity against beta-glucuronidase and significant inhibition of experimental pulmonary metastasis of the highly metastatic melanoma B16.

Kawase et al (Kawase et al., 1995, J. Antibiotics 49: 61-64) describes inhibitory activities of A-72363 A-1, A-2 and C, the diastereomers of siastatin B, against various glycosidases. A-72363 C inhibited bovine liver beta-glucuronidase and tumor cell heparanase with IC50 values of 1.6 μM and 12 μM, respectively.

Fungal metabolites such as derivatives isolated from the fungal strain *Acremonium* sp. MT70646 were described by Ko et al. (Ko et al., 2000, J. Antibiot (tokyo) 53:211-4) and in WO 01/46385, which discloses positive results obtained for CRM636-B (produced by said fungi) in inhibiting angiogenesis and B16 melanoma cell invasion.

Shiozawa et al describe the chemical and biological activities of trachyspic acid, a small molecule metabolite isolated from the culture broth of Talaromyces trachyspermus that inhibited heparanase (Shiozawa et al., 1995, J Antibiot (Tokyo). 48:357-62).

Heterocyclic compounds such as phthalimide carboxylic acid derivatives are described in WO 03/74516 to Courtney et al. This international application, which was granted a US patent (US 7,138,425) on November 2006, describes

heparanase inhibition and anti-angiogenesis activity of 17 phthalimide carboxylic acid derivatives. Please note that this patent was granted for the new small molecule inhibitors based on *in vitro* and *ex-vivo* data only (!). No *in vivo* tests are described in the patent.

Heparanase inhibitors of different chemical structures have been also described in the International PCT Applications WO 02/060373, WO 02/060374, WO 02/060375, and WO 02/060867, of the same applicants: WO 02/060373 discloses indole derivatives as heparanase inhibitors and describes the inhibition of mouse melanoma primary tumor growth and of metastasis induced by these indole derivatives.

WO 02/060374 discloses benz-1,3-azoles, more derivatives as heparanase inhibitors, and inhibition of mouse melanoma primary tumor growth and of metastasis by these compounds. For some compounds, the results were striking.

WO 02/060375 discloses diphenyl ether derivatives as heparanase inhibitors. Inhibition of mouse melanoma primary tumor growth is described.

WO 02/060867 discloses carbazole and fluorene derivatives as heparanase inhibitors. Inhibition of angiogenesis, mouse melanoma primary tumor growth and of metastasis is described.

All four WIPO publications disclose data regarding enzymatic inhibition and angiogenesis inhibition by the small molecule inhibitors, as well.

The art in the year the present application was filed (2004), discloses further small molecules active as heparanase inhibitors. For example benzoxazole, benzthiazole and benzimidazole derivatives are disclosed in WO 04/0466122 and WO 04/046123, and furanthiazole derivatives are disclosed in WO 04/013132. Tetronic acid derivatives are disclosed in Ishida et al., 2004, and phthalimide carboxylic acid derivatives are described by Courtney et al, 2004, both of which were mentioned by the examiner.

The development of heparanase inhibitors has been reviewed by Ferro et al (Ferro et al, 2004, Mini Rev. Med. Chem. 4(6):693-702). The identification of inhibitors of heparanase is described as an attractive approach towards developing new therapeutics for metastatic tumors and chronic inflammatory diseases. The review focuses on small molecule heparanase inhibitors that have been isolated or synthesized up to 2004, and discusses the more recent (namely, as of 2004) developments in the understanding of heparanase structure and function that may ultimately aid in the future design of inhibitors with improved potency and specificity.

Another more recent review by Hammond et al (Hammond et al, 2006, New Developments in Therapeutic Glycomics 251-

282), mentions a wide spectrum of small molecule inhibitors, including those of the present invention (reference 138 in Hammond et al). Hammond et al define the compounds of the present invention as a new series of heparanase inhibitors bearing long alkyl chains, which is a common structural feature to several other known heparanase inhibitors such as trachyspic acid, RK-682, CRM464-A mentioned above. Some compounds (e.g. compound 1 of the present application) are mentioned as effective inhibitors of *in vitro* cell invasion.

Hammond et al further list patent applications, which describe several classes of aromatic compounds that inhibit heparanase with μM IC_{50} values. The compounds were separated into four classes: diphenyl ether derivatives (IC_{50} = 5-45 μM), carbazole and fluorine derivatives (IC_{50} = 8-25 μM), indole derivatives (IC_{50} = 10-26 μM) and benz-1,3-azole derivatives (IC_{50} = 1.5-36 μM). Compounds from each of the classes are reported to significantly inhibit metastasis and/or primary tumor growth in B16-F1 mouse melanoma models.

Regarding sulfated polysaccharide inhibitors, Hammond et al state that the development of heparanase inhibitors that are large and highly charged, and therefore similar to the HS substrate, has met with some success although such compounds are not orally bioavailable and this complicates their administration. The properties of these

poly-and oligosaccharides and their mimetics are barriers to oral administration.

Courtney et al, cited by the examiner, disclose that in animal models treatment with heparanase inhibitors has been shown to markedly reduce the incidence of metastasis, and therefore heparanase offers an attractive drug target. However the repertoire of inhibitors available at that time was very limited and confined mainly to polysulfonated oligosaccharides, such as the clinically tested PI-88. Nevertheless, according to Courtney et al, this inhibitor had serious disadvantages since it presented a multifunctional profile, potentially complicating an understanding of its mode of action.

As an alternative, Courtney et al disclose a series of 46 potent and selective small molecules inhibitors derived from 2,3-dihydro-1,3-dioxo-1*H*-isoindole-5-carboxylic acid, which may provide useful biological tools for unraveling the complex biology of heparanase and which may serve as basis for the design of novel therapeutic agents. The *in vitro* inhibition of heparanase and ant-angiogenic activity of these derivatives are disclosed in Tables 1-4 of Courtney et al.

Ishida et al disclose an efficient visual method for screening heparanase inhibitors. According to Ishida et al, "An obstacle to high-throughput screening has hampered the search for heparanase inhibitors from a large number of

natural sources or chemical libraries." That is the reason, according to Ishida et al, why "most heparanase inhibitors reported by now are derivatives of sulfated oligosaccharide similar to the substrate HS, and not low molecular weight compounds".

Thus, contrary to the examiner's interpretation of Ishida et al, small molecule inhibitors were not reported by then because there was no efficient screening methods to detect them and NOT because said small molecules have been found unsuitable as heparanase inhibitors. In the Discussion section (pages 140-141) of Ishida et al, it is stated:

> "Reports on the search for heparanase inhibitors have been limited by the instability of the protein and the difficulty of assay. To overcome this problem, we established heparanase-expressing stable clones by transfection to HepG2 cells. We also innovated on visual and facile screening method using a novel HS-containing polyacrylamide tablets for dealing with massive samples...After activity guided purification...the known compound RK-682 was identified as the active substance...the usefulness of the bioassay was proven because RK-682 and its 4-Benzyl-derivative were identified as heparanase inhibitors."

The structure of RK-682 and its derivative are depicted in Fig 4A, page 140, and one can clearly see that these inhibitor (IC_{50} 17μM) are indeed small molecules and not sulfated oligosaccharides.

McKenzie reviews the development of the Oxford GlycoSciences (OGS) heparanase series of compounds, and presents the analysis of derivatives of 2,3-dihydro-1,3-dioxo-

1*H*-isoindole-5-carboxylic acid (also disclosed by Courtney et al) as a case study example of the structure-activity relationship (SAR) involved in the progression of this class of drugs towards animal model testing. McKenzie mentions that "Between 1999 and 2003, OGS undertook a program aimed to develop small-molecule inhibitors against heparanase enzyme activity" since "it is envisaged that these inhibitors will serve as valuable research tools for both in vitro and in vivo studies into the functioning of the enzyme in both normal and disease settings."

The ultimate analysis employed for the OGS compounds were efficacy in the primary enzyme assay (i.e. inhibition of heparanase) and secondary cell-based angiogenesis assay. McKenzie indicated on page 7, end of the first paragraph in the left column, that:

> "Overall, it is likely that these compounds will be useful as biological tools to dissect the function of heparanase enzyme in both normal and disease settings. Unfortunately, there is no published data on the efficacy of any of the OGS small molecule inhibitors in animal studies, hence it remains to be seen whether these compounds will actually have efficiency in vivo".

Please note that McKenzie is not accurate when stating that there is no published data on the efficacy of any of the small molecule inhibitors in animal studies, since as pointed out above, at least Nishimura et al and the four PCT publications WO 02/060373, WO 02/060374, WO 02/060375, and WO

02/060867, present inhibition of mouse melanoma primary tumor growth and/or inhibition of metastasis by certain small molecule heparanase inhibitors.

McKenzie also seems to have missed the paper by Pan et al (Pan et al, 2006, Bioorg Med Chem Lett. 16(2):409-12), that discloses 1-[4-(1H-Benzoimidazol-2-yl)-phenyl]-3-[4-(1H-benzoimidazol-2-yl)-phenyl]-urea derivatives as small molecule heparanase inhibitors and their evaluation *in vivo* in the B16 melanoma metastasis model. According to Pan et al, results obtained with one derivative (identified as 7a) showed around 50% inhibition of lung metastasis, which is comparable to the result obtained from PSS, a very potent sulfated poly saccharide heparanase inhibitor. A copy of Pan et al is attached.

Another paper by the same group, Xu et al (Xu et al, 2006, Bioorg Med Chem Lett. 16(2):404-8) discloses identification of "proof of concept" small molecule heparanse inhibitors, a novel class of N-(4-{[4-(1H-benzoimidazol-2-yl)-arylamino]-methyl}-phenyl)-benzamide, with efficacy in animal model. Xu et al disclose that experiments in mice with two very potent derivatives show that they orally bioavailable. Changing the route of administration to intraperitoneal dosing did not lead to increased plasma exposure. The rejection is therefore clearly wrong in alleging that the prior art does not disclose small molecules as haparanase inhibitors.

Applicants would like to conclude thus far by quoting Dr. Joel van Gelder, who is one of the main inventors of the present invention and a recognized expert in the field of heparanase inhibitors:

> "From the arguments mentioned by the examiner, I do not understand why he distinguishes between small molecules and sulfated oligosaccharides such as PI-88. In fact, PI-88 is the best example of a correlation between inhibition of heparanase in vitro, its in vivo effect in animals and positive clinical studies. This correlation has nothing to do with the chemical structure of the inhibitor.
>
> In most cases, the common pharmacophore for the variety of small molecule heparanase inhibitors described in the art, is a heterocyclic moiety with at least one hydrogen bond acceptor and an acidic group (one sulfonic acid or two carboxylic acids) in order to interact with one of the heparin-binding domains of heparanase and a long chain (n>14) which will be positioned into the large groove of heparanase and block the catalytic activity of heparanase. Our inhibitors have some structural similarity (a heterocyclic moiety with a long alkyl chain) with the fungal metabolite CRM636-B, trachyspic acid and RK-682, but our inhibitors are much more potent.
>
> It is not easy to find a correlation between inhibition of invasion in vitro and an anti-metastatic effect in vivo since only a few in vivo metastasis models and anti-metastatic agents exist."

2. The breadth of the claims

The examiner asserts that the elected claims, e.g., claims 1, 16 and 17, "are very broad and recite the treatment of broad genus of disease with a broad genus of compounds. Others, such as claim 18 are narrower, reciting specific

species of the claimed genus of compounds, but still claiming a broad genus of diseases."

Applicants have provided ample reasoning and explanation above, showing that the application is enabling with respect to treatment of cancers in general, namely, the small molecule inhibitors are not specific to a particular type of cancer, but rather act on and affect a **mechanism** (cell invasiveness and angiogenesis), which is common to most types of cancer.

Applicants have also explained that positive results obtained in enzymatic assay (inhibition of heparanase with a relatively low IC_{50} values), a cell invasion assay and/or a cell-based angiogenesis assay, are considered in the art (see McKenzie above) sufficient enough to progress the screened inhibitors towards *in vivo* tests and then further towards clinical trials. Since the present application teaches various relevant assays to show suitability of the compounds of the invention as heparanase inhibitors, and since the result of enzymatic inhibition and invasiveness assays are provided in the application in Appendix A, the present application should be considered enabling with respect to the whole scope of inhibitors disclosed therein, as well as with respect the diseases listed in the claims.

3. The amount of direction or guidance provided and the presence or absence of working examples

The examiner stated: "The specification only provides *in vitro* heparanase inhibition data for compounds 1-107. There is no animal data to corroborate that these compounds will have efficacy in animals, even less in humans. The specification provides no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration routes, etc) necessary to treat melanoma with compound 106. The directions concerning treating cancer (melanoma) are found in the specification at pages 41-44 and 64-68, which merely states Applicants' intention to do so by providing *in vitro*, *ex vivo* and *in vivo* assays, but no compounds were actually tested in those assays, except for the in vitro heparanase inhibition mentioned at the beginning of this paragraph."

Contrary to the examiner's assertion, the present application provides *in vitro* assay of cell invasion inhibition by heparanase inhibitors, in addition to the enzymatic inhibition assay. Second, precise direction and guidance is provided in the description for determining the particular administration regimens for use of any of the candidate compounds for treatment of any type of cancer and metastasis thereof, which can be affected by inhibition of

angiogenesis and cancerous cell migration, including treatment of melanoma. Thus, it is stated in the paragraph bridging pages 47 and 48 of the description (emphasis added):

> "The amount of the therapeutic or pharmaceutical composition of the invention which is effective in the treatment of a particular disease, condition or disorder will depend on the nature of the disease, condition or disorder and can be determined by standard clinical techniques. In general, the dosage ranges from about 0.01 mg/kg to about 50-100 mg/kg. In addition, in vitro assays as well as in vivo experiments may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease, condition or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. For example, in order to obtain an effective mg/kg dose for humans based on data generated from mice or rat studies, the effective mg/kg dosage in mice or rats is divided by twelve or six, respectively."

The test are clearly routine!

In addition, as applicants have stated above, the Examiner has no authority to in effect require that clinical trials be conducted and used as evidence to provide enablement for method of treatment claims. The description provides guidance and test results for the *in vitro* heparanase activity assay, and detailed teaching of *in vivo* assay using the primary melanoma tumor model which can serve for evaluation of effective doses as taught in the cited paragraph above.

4. The quantity of experimentation necessary

The examiner, holding the position that the art is unpredictable and there is absence of experimental evidence commensurate in scope with the claims, is of the expressed opinion that the skilled artisan would not accept that the claimed compound 106 could be predictably used as treatment for melanoma. The examiner argues: "Since there is no precedent in the literature for the treatment of melanoma with any of the claimed compounds or similar compounds, how is the skilled physician supposed to know how to dose this compound in order to treat melanoma? Determining if the claimed compound 106 (or any of the non-elected compounds) would treat melanoma (or any particular cancerous disease) would require formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicant".

To the contrary, and respectfully, applicants have shown above that the present art is sufficiently predictable with respect to the use of small molecule heparanase inhibitors for the inhibition of melanoma tumor growth and metastasis formation. Once a person skilled in the art has read applicants' disclosure, applicants' invention would be readily understood and accepted based on conventional

knowledge in the art at the time of applicants' effective filing date. Of course, further experiments would be necessarily carried out on human subjects, but these would only be routine, i.e. the type of further experiments which are fully acceptable under the first paragraph of section 112.

To the extent that the PTO would demand that experiments in humans have to be presented or at least be shown to exist in the art for related compounds to meet the requirements of Section 112 is simply not the law, and, respectfully, is unacceptable and not logical. Such a requirement is beyond the authority of the PTO. As applicants have shown above, for the purpose of evaluating new drug candidates, even *in vitro* test results, such as those presented, form established *in vitro* model systems which are fully satisfactory to meet the requirements of Section 112.

Withdrawal of the rejection is in order and is respectfully requested.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that

should lead to patentability of the present application.

Favorable consideration and early formal allowance are respectfully requested.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By _____
Sheridan Neimark
Registration No. 20,520

SN:tdd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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